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Hepatoprotective and Antihyperglycemic Effects of Sea Grapes (*Caulerpa spp.)* as a Potential Therapeutic Approach for NAFLD and NASH

Yasmin Azzahra Arifin[1], Annette d'Arqom[2*]

[1] Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60131, Indonesia.

[2]Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, 60131, Indonesia.

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) and its advanced form, non-alcoholic steatohepatitis (NASH), are increasingly prevalent metabolic liver disorders characterized by hepatic lipid accumulation, oxidative stress, inflammation, and insulin resistance. Despite their global burden, effective pharmacological treatments remain limited, which highlights the need for safe and multi-targeted natural alternatives. This literature review summarizes current evidence from *in vitro, in vivo,* and early clinical studies investigating the hepatoprotective and antihyperglycemic properties of *Caulerpa spp*., including *C. lentillifera*, *C. racemosa*, *C. taxifolia,* and *C. prolifera.* The review focuses on research published between 2015 and 2025 related to *Caulerpa* bioactivity, liver protection, glucose regulation, oxidative stress, lipid metabolism, and gut microbiota modulation. Across the reviewed studies, *Caulerpa*-derived bioactive compounds such as polysaccharides, carotenoids, peptides, and polyphenols consistently demonstrated hepatoprotective and metabolic benefits. Supplementation improved antioxidant enzyme activities, including superoxide dismutase, catalase, and glutathione, while reducing malondialdehyde levels, thereby protecting hepatocytes from oxidative damage that contributes to NAFLD progression. Several studies also reported downregulation of lipogenic genes such as SREBF1, FAS, and ACC, together with activation of SIRT1 and AMPK signalling pathways, which reduced hepatic triglyceride accumulation. Extracts from *C. taxifolia* and *C. prolifera* exhibited strong alpha-amylase and alpha-glucosidase inhibition, improving glucose regulation. In addition, Caulerpa supplementation was shown to restore intestinal barrier integrity and modify gut microbiota composition, leading to lower endotoxin levels and reduced hepatic inflammation. The only available human clinical trial demonstrated a significant reduction in fasting glucose following *C. racemosa* supplementation, supporting its potential for clinical application. Overall, the evidence indicates that *Caulerpa* species exert multi-pathway hepatoprotective and antihyperglycemic effects. However, further studies are required to standardize extract preparation, determine optimal dosage, and assess long-term safety. *Caulerpa* spp. demonstrates promising preclinical potential. However, further translational research and rigorous clinical trials are warranted to validate these findings and determine its feasibility as a nutraceutical for NAFLD, NASH, and metabolic syndrome.

Keywords: *Caulerpa spp*, Sea grapes, Hepatoprotective, Anti hyperglycemic, Fatty liver disease, Metabolic syndrome

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and its more severe form, non-alcoholic steatohepatitis (NASH), are major global health problems linked to obesity, insulin resistance, and type 2 diabetes. Affecting nearly one-third of the world's population, NAFLD is considered the hepatic manifestation of metabolic syndrome, characterized by excessive lipid accumulation in hepatocytes independent of alcohol consumption. Persistent hepatic steatosis can progress to chronic inflammation, fibrosis, and cirrhosis, posing a significant risk for hepatocellular carcinoma. The underlying mechanisms of NAFLD and NASH involve oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and dysregulation of lipid and glucose metabolism

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

[3][6]. Despite the high prevalence of NAFLD, current pharmacological treatments remain limited. Management strategies largely depend on diet and lifestyle modification, as no approved first-line drugs are available. Therefore, natural marine-derived compounds with antioxidant, metabolic, and gut-modulating effects are attractive alternatives. *Caulerpa spp.* are unique among green macroalgae due to their high sulfated polysaccharide and carotenoid content, which have shown strong metabolic regulatory activity in recent preclinical studies Species such as *C. racemosa, C. lentillifera, C. taxifolia, and C. prolifera* contain a rich array of bioactive compounds. Preclinical evidence suggests these compounds hold therapeutic promise. Experimental studies, using both *in vivo* animal models and in vitro cell lines, have shown that *Caulerpa* extracts can modulate key molecular pathways associated with lipid metabolism and energy balance, such as the SIRT1/AMPK and mTOR signaling cascades. Furthermore, emerging research highlights mechanisms central to NAFLD/NASH pathophysiology, including the inhibition of digestive enzymes like α-amylase, the suppression of oxidative stress, and the modulation of the gut-liver axis through changes in gut microbiota composition [3][5][7][9].

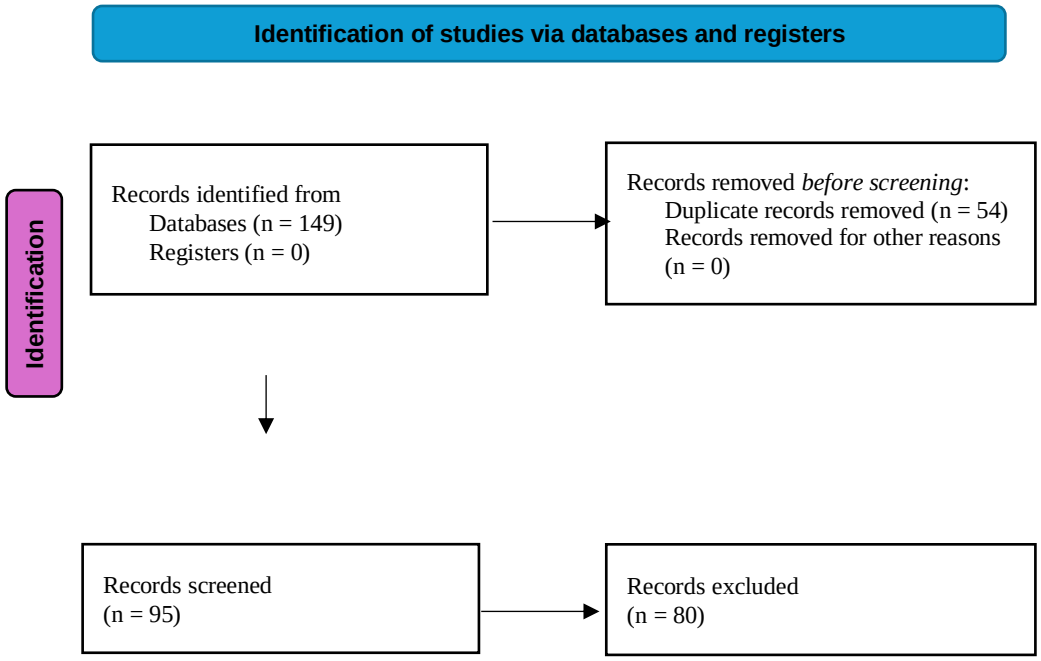
This review therefore aims to synthesize and analyze recent findings on the hepatoprotective and antihyperglycemic effects of sea grapes (*Caulerpa spp.)* and relating to NAFLD and NASH treatment. By integrating biochemical, molecular, and microbiome perspectives, this paper provides a comprehensive understanding of how *Caulerpa*-derived compounds contribute to metabolic and hepatic protection, establishing a foundation for future nutraceutical development and clinical translation.

MATERIAL AND METHOD

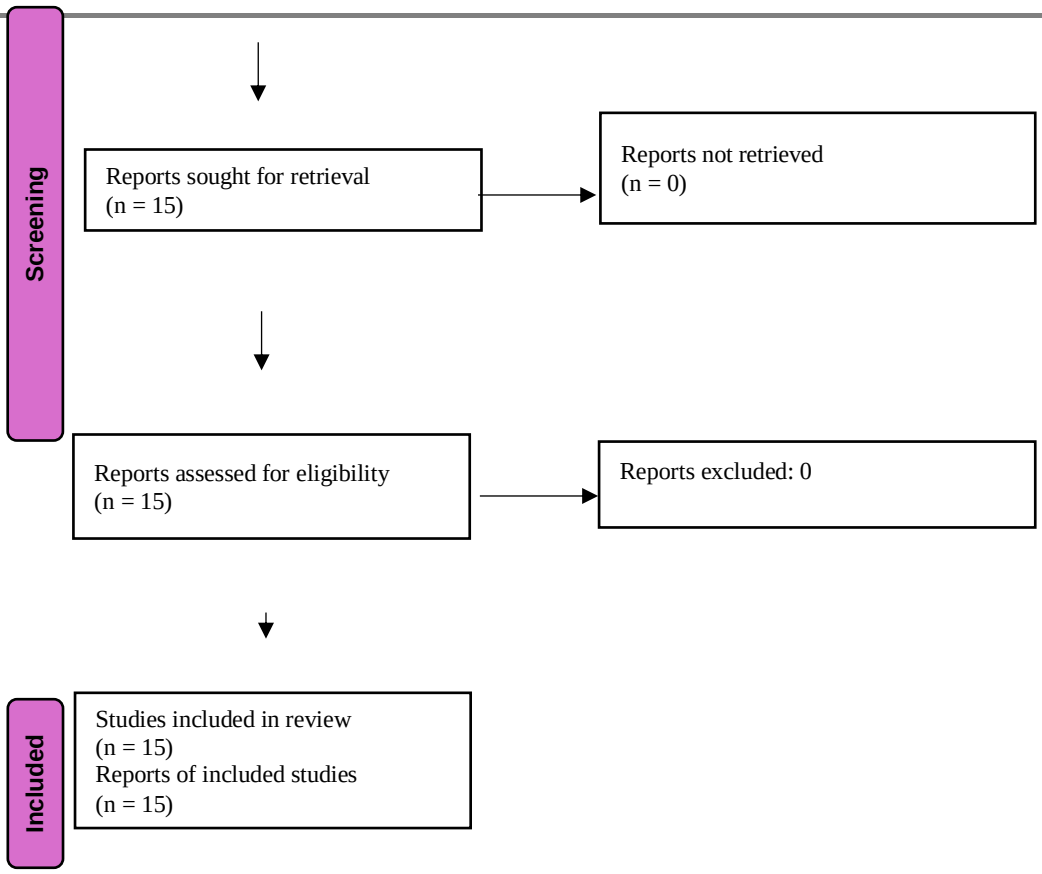
Research Strategy

A structured literature search was conducted in Scopus (Elsevier) and PubMed using the keyword phrases “Sea grapes” OR “*Caulerpa*” OR “*Caulerpa lentillifera*” OR “Macroalgae” AND “Liver disease” OR “NAFLD” OR “NASH” OR “Liver steatosis” OR “Fatty liver disease.” OR "blood glucose" OR "anti diabetic" OR "blood sugar regulation" The search was performed on 5 November 2025 (Asia/Surabaya) and limited to publications from 2015–2025. The initial query returned 95 for Scopus (Elsevier). Titles and abstracts were screened for relevance to the hepatoprotective and blood glucose-lowering effects of sea grapes for treating NAFLD and NASH. Only English-language publications were included. After applying these criteria, 15 studies were retained for full-text review and included in this narrative literature review. The detailed study selection process, outlining study identification, screening, eligibility, and inclusion, is summarized in the PRISMA 2020 Flowchart (See Figure 1)

Figure 1 Prisma Flowchart



ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025



Inclusion and Exclusion Criteria

Inclusion criteria: Articles published between 2015–2025, written in English, involving *Caulerpa spp.* or sea grapes (including extracts or isolated bioactive compounds), and reporting hepatoprotective and/or antihyperglycemic effects in NAFLD, NASH, fatty liver disease, liver steatosis, insulin resistance, or hyperglycemia in *in vivo*, *in vitro*, or clinical studies Exclusion criteria: Non-English publications; articles without liver- or glucose-related outcomes; studies on algae not belonging to *Caulerpa* spp., reviews, editorials, or conference abstracts without primary data, studies focusing only on chemical composition without biological activity, and studies unrelated to metabolic or liver disease models.

Quality and Risk-of-Bias Assessment

The methodological quality of the included studies was independently assessed by reviewers. The risk-of-bias for *in vivo* (animal) studies was conducted using criteria from the SYRCLE (Systematic Review Centre for Laboratory animal Experimentation) checklist. For the single clinical trial, the Cochrane Risk-of-Bias 2 (RoB 2) tool was used. *In vitro* studies were assessed using the SciRAP (Science in Risk Assessment and Policy) method, which evaluates both reporting quality and methodological quality based on predefined criteria such as clarity of test system description, exposure characterization (e.g., concentrations), adequacy of controls, and replication. Any disagreements in assessment were resolved through discussion or consensus. The results of this risk-of-bias assessment are summarized and integrated into the synthesis tables (Tables 1-3).

Data Extraction and Synthesis

From the 15 studies, we extracted aggregate data on study design (e.g., *in vivo* animal model, *in vitro* cell culture, or human clinical trial), sample characteristics (e.g., species, strain, or participant demographics), and intervention specifics (e.g., *Caulerpa* species, extract type, dosage, and duration). Key outcome measures were categorized by hepatoprotective effects (including changes in liver enzymes, hepatic fat accumulation, oxidative stress markers, and fibrosis) and antidiabetic effects (including fasting blood glucose, enzyme inhibition, insulin levels, and metabolic regulators like PGC-1). Evidence was synthesized narratively, with harmonization of effect measures where feasible. No meta-analysis was performed due to the significant heterogeneity observed across

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

study models, intervention protocols, and outcome measures. Although a meta-analysis was not performed, the narrative synthesis includes an evaluation of the overall strength of evidence based on an adapted GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework. The strength of evidence was categorized as 'high', 'moderate', 'low', or 'very low' based on study risk of bias, consistency of findings, and the precision of the reported preclinical data.

RESULT AND DISCUSSION

Hepatoprotective Effects of *Caulerpa* spp.

Multiple studies demonstrate *Caulerpa* spp, possess notable hepatoprotective activities, primarily through enhancing endogenous antioxidant defenses, reducing hepatic inflammation, and restoring liver enzyme balance. In a diquat-induced liver injury model, supplementation with *Caulerpa lentillifera* significantly decreased ALT levels (from approximately 29 U/mg to 20 U/mg) while increasing SOD activity (from 38 U/mg to 46 U/mg), indicating an effective reduction of oxidative stress within hepatocytes [1]. Comparable protective outcomes were observed in ethanol-induced liver injury, where *C. lentillifera* administration alleviated elevations in AST and GGT and lowered hepatic inflammation scores. These benefits were accompanied by suppression of TLR4-mediated inflammatory signaling and recovery of intestinal tight-junction proteins such as occludin and ZO-1 [5]. In high-fat diet (HFD) animal models, sulfated polysaccharides derived from *C. racemosa* significantly decreased oxidative stress markers and enhanced the activity of endogenous antioxidant enzymes, further confirming its hepatoprotective potential [7]. Supplementation with *C. lentillifera* in animals with metabolic syndrome similarly improved hepatic SOD activity and reduced lipid accumulation in liver tissue [10]. Since oxidative stress plays a central role in the development and progression of NAFLD, these consistent findings suggest that *Caulerpa* supplementation may prevent early hepatocellular damage and slow the transition to steatohepatitis.

Antihyperglycemic and Metabolic Effects

The reviewed studies also reveal strong antihyperglycemic effects across different *Caulerpa* species. A sulfated galactan isolated from *C. taxifolia* improved insulin sensitivity, reduced fasting blood glucose, and inhibited α-amylase activity in diabetic mice [3]. Polyphenolic extracts of *C. prolifera* demonstrated potent α-glucosidase and α-amylase inhibition in vitro, with compounds such as vanillin and kaempferol showing strong enzyme-binding affinity [4]. *In vivo* studies confirmed glucose-lowering effects, as *C. racemosa* supplementation significantly reduced blood glucose levels in obese and high-fat diet animal models [9,12], while *C. lentillifera* improved glucose profiles in metabolic syndrome rats [10]. Notably, the only available double-blind, placebo-controlled human trial demonstrated that 4-week supplementation with *C. racemosa* significantly reduced mean fasting blood glucose in obese adults, from a baseline of 113.68 mg/dL to 79.82 mg/dL ($p=0.000$) [11].These findings suggest that *Caulerpa* acts through multiple mechanisms, including enzyme inhibition, increased insulin sensitivity, and improved hepatic glucose metabolism.

Comparison on *Caulerpa* spp.

Although hepatoprotective and antidiabetic effects were observed across all species, different *Caulerpa* types demonstrated distinct therapeutic strengths. *C. lentillifera* consistently showed antioxidant and anti-steatosis activity, preventing hepatic lipid accumulation and reducing oxidative injury in zebrafish, rats, and HepG2 cells [1,5,6]. *C. racemosa* produced the strongest antihyperglycemic effects in both preclinical and clinical studies and significantly improved gut microbiota composition in high-fat diet models [7,9,11]. *C. taxifolia* and *C. prolifera* exhibited potent α-amylase and α-glucosidase inhibition due to high phenolic and polysaccharide content [3,4]. These differences suggest the possibility of species-specific application, where *C. lentillifera* may be more suitable as an antioxidant hepatoprotective agent, while *C. racemosa* and *C. taxifolia* may serve as effective glucose-lowering and metabolic regulators.

Table 1 Summary Of *In Vitro* Studies on The Metabolic Effects of *Caulerpa* Spp.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

Study (Author, Year)	*Caulerpa* Species	Model Cell / Assay	Key Finding	Mechanism	Risk of Bias Assessment
Sangpairoj et al. (2024)	*C. lentillifera*	HepG2 hepatocytes; assays: MTT cytotoxicity, Oil Red O staining, Triglyceride assay, qPCR, Western blot	↓Lipid accumulation; ↓Trigliserida	↑ SIRT1/AMPK Pathway, ↓Lipogenesis genes (SREBF1, FAS, ACC) Potential binding of major compounds (dl-2-phenyltryptophane, benzoic acid) to SIRT1 and AMPK (via docking)	Low Risk
Ouahabi S. et al. (2025)	*C. prolifera*	Assay α - mylase & α-glucosidase	Strong inhibitory activity; some extracts (ME, AQE) comparable or superior to acarbose	Digestive enzyme inhibition (slower carb breakdown & glucose absorption	Low Risk
		DPPH & β-carotene bleaching	Aqueous/methanolic extracts show strong radical scavenging; EA strongest in lipid peroxidation inhibition	Antioxidant activity (radical scavenging & lipid oxidation inhibition)	Low Risk
Dissanayake, I.H et al. (2022)	*C. racemosa*	DPPH, FRAP	Moderate–strong antioxidant activity; strong correlation with phenolic & flavonoid content	Free-radical scavenging & reducing activity	Low Risk
		α-amylase & α-glucosidase inhibition; Anti-glycation assays	Strong inhibition of α-amylase (CPE) and α-glucosidase (EA fraction); clear dose–response; notable anti-glycation effects	Digestive enzyme inhibition → potential postprandial glucose control	Low Risk
Nurkolis et al. (2023)	*C. lentillifera*	HepG2 hepatocytes (lipid accumulation assays)	↓Lipid accumulation; ↓TG; ↑SIRT1/AMPK	Lipid-lowering via SIRT1–AMPK activation	Moderate Risk

Table 2 Summary of *In Vivo* (Animal Model) Studies on The Hepatoprotective And Antidiabetic Effects of *Caulerpa* Spp

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

Study (Author, Year)	*Caulerpa* Species	Animal Model	Dose	Duration	Key Findings (Liver & Glucose)	Risk of Bias Assessment
Lin X et al. (2024)	*C. lentillifera* (Dried powder)	Zebrafish (Danio rerio) (Diquat-induced oxidative damage)	20 g/kg & 50 g/kg in diet	56 days	Glucose: ↓ Blood Glucose ↑ glut2 & akt mRNA (Insulin signaling) Liver: ↓ Liver MDA (Oxidative stress) ↑ SOD activity (Antioxidant) ↓ ALT & AST (Liver enzymes) ↓ Hepatic TG ↓Histopathological lesions	Medium Risk
Kurniawan, R. et al. (2025)	*C. racemosa* (Carotenoids) & *C. lentillifera* (Peptide).	Male Rattus norvegicus fed a CFED	22.5 mg/kg & 45 mg/kg BW	4 weeks	Glucose & Metabolism: ↓ Blood Glucose ↓ α-glucosidase & α-amylase activity ↓ Lipase activity Liver & Lipids: ↓ TG, TC, LDL ↑ HDL ↓ AST (Liver enzyme) ↓ TNF-α, ↑ IL-10	Low Risk
Liu, S. et al. (2025)	*C. taxifolia* (Sulfated galactan - SGC)	Male C57BL/6J mice (T2DM	100, 200, 400	5 weeks	Glucose & Insulin: ↓ Fasting Blood	Medium Risk

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

		model)	mg/kg/day		Glucose ↓ HOMA-IR (Insulin Resistance) ↑ Glucose Tolerance (OGTT) Liver & Oxidative Stress: ↓ Liver damage (vacuolation) ↑ Antioxidants (SOD, CAT, GSH) ↓ MDA (Oxidative stress marker)	
Lin K.Y. et al. (2023)	*C. lentillifera* (Dried powder)	Male Wistar rats (Chronic ethanol exposure)	5% in liquid diet (8.4 g/L)	12 weeks	Glucose: No glucose data measured. Liver & Gut: ↓ Serum AST & GGT ↓ Liver inflammation score ↔ Liver steatosis, Hepatic TC & TG (No change) ↓ Circulatory endotoxin ↓ Hepatic TNF-α & IL-1β ↓ TLR4 pathway (Inflammation) ↑ Intestinal Occludin & ZO-1 ↓ F/B ratio; ↑ Akkermansia	Low Risk
Mayulu, N. et al. (2023)	*C. racemosa* (Sulfated Polysaccharide - SPCr)	Male Rattus norvegicus fed a CFED	65 & 130 mg/kg BW	6 weeks	Glucose & Metabolism: ↓ Blood Glucose	Medium Risk

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

					(High dose most effective) ↓ Serum Lipase & Amylase Liver & Lipids: ↔ AST & ALT (No significant change) ↓ HMG-CoA Reductase ↑ SOD Cardio	
Nurkolis et al. (2023)	*C. racemosa* (Aqueous extract - AEC)	Male albino Swiss mice fed a CFED	65 & 130 mg/kg BW	6 weeks	Glucose & Metabolism: ↓ Blood Glucose ↓ Serum Amylase & Lipase Liver & Lipids: ↓ TG, TC, LDL; ↑ HDL ↑ Cardio SOD ↓ PRMT-1 & ADMA (Cardiometabolic markers)	Medium Risk
Manoppo, J.I.C. *et al.* (2022)	*C. lentillifera* (Extract)	Male Rattus norvegicus fed a CFED	150 & 450 mg/kg BW	4 weeks	Glucose: ↓ Blood Glucose Liver & Lipids: ↓ Total Cholesterol ↑ Liver SOD (Antioxidant) ↑ PGC-1α (Mitochondrial biogenesis)	Medium Risk
Kuswari M. et al. (2021)	*C. racemosa* (Extract)	Male Wistar albino rats fed a CFED	150 & 450 mg/kg BW	4 weeks	Glucose: ↓ Blood Glucose (150 mg/kg > 450 mg/kg)	High Risk

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

					Liver & Lipids: ↓ Total Cholesterol	
Cao, M. et al. (2021)	*C. racemosa* (Polysaccharide extract - PCR)	Male Wistar albino rats (Diabetic Nephropathy: high fructose + STZ)	100 & 400 mg/kg BW	8 weeks	Glucose & Insulin: ↓ Fasting Blood Glucose ↑ Serum Insulin Liver/Kidney (Hepatoprotective): ↓ Serum TC, TG, LDL-C ↓ Renal MDA (Oxidative stress) ↑ Renal Antioxidants (SOD, CAT, GSH-Px) ↓ Renal Cytokines (IL-1β, IL-6, TNF-α) ↓ Renal Fibrosis & Lesions	Medium Risk
du Preez, R et al. (2020	*C. lentillifera* (Dried, whole)	Male Wistar rats fed High-Carb High-Fat diet	5% in diet	8 weeks	Glucose: ↔ Basal Blood Glucose (No reduction) ↔ Glucose Tolerance (No improvement) Liver & Lipids: ↓ Liver Fat Deposition & Inflammation ↔ Plasma ALT & AST (No change) ↓ Total Cholesterol & NEFA	Medium Risk
Sharma et al. (2015)	*C.lentillifera* (Ethanol extract - CLE)	C57BL/KsJ-db/db mice (Genetic T2DM)	250 & 500 mg/kg BW	6 weeks	Glucose & Insulin: ↓ Fasting Blood Glucose ↑ Glucose & Insulin Tolerance (OGTT/IPITT) ↓	Medium Risk

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

					HOMA-IR Liver & Metabolism: ↑ Hepatic Glycogen ↑ GK activity, ↓ G-6Pase activity	

Table 3 Summary of Clinical (Human) Studies on The Metabolic Effects of *Caulerpa* Spp.

Study (Author, Year)	*Caulerpa* Species	Study Design	Participants (n)	Dose	Duration	Key Quantitative Findings	Risk of Bias Assessment
Permatasari et al. (2022)	*C. racemosa*	RCT, double-blind, placebo-controlled clinical trial	69 obese men (BMI 25–30 kg/m²) completed the study (35 in extract group, 34 in placebo group)	1.68 g/day of sea grape extract or placebo	4 weeks	↓ Blood Glucose: Significantly lower ($p<0.0001$) compared to placebo ↑ PGC-1α: Significantly higher ($p=0.000$) compared to placebo	Some Concerns

Caulerpa spp. as a Potential Therapy for NAFLD and NASH

Non-alcoholic fatty liver disease (NAFLD) progresses to non-alcoholic steatohepatitis (NASH) through a series of interrelated metabolic and inflammatory disturbances. Persistent insulin resistance promotes excessive delivery of free fatty acids to the liver and stimulates de novo lipogenesis via regulatory factors such as SREBP-1c, FAS, and ACC, resulting in hepatocellular triglyceride accumulation and lipotoxicity [16][17]. As lipid burden increases, mitochondrial β-oxidation becomes impaired, generating reactive oxygen species and lipid peroxidation products such as malondialdehyde. These oxidative insults induce hepatocyte injury and activate inflammatory cascades, including TLR4–NF-κB signaling, which further amplify cytokine production and immune cell recruitment [16][19]. Concurrently, gut dysbiosis and disruption of intestinal barrier function increase endotoxin translocation into portal circulation, promoting hepatic inflammation, stellate-cell activation, and fibrogenesis through the gut–liver axis [17][18]. Collectively, lipid overload, oxidative stress, inflammation, and microbiome-mediated hepatic injury constitute the major mechanisms driving progression from simple steatosis to NASH.

Within this pathogenic framework, evidence from *in vitro* and *in vivo* studies demonstrates that species of *Caulerpa* exert hepatoprotective and antihyperglycemic effects through multiple biochemical pathways. *Caulerpa lentillifera* supplementation has been shown to restore endogenous antioxidant defense systems. For instance, in a diquat-induced zebrafish model, 50 g/kg supplementation restored the protective enzyme SOD activity (from ~38 U/mg to ~46 U/mg) while concurrently lowering the liver damage marker ALT (from ~29 U/mg to ~20 U/mg). In zebrafish and HepG2 hepatocyte models, *C. lentillifera* downregulated SREBF1, FAS, and ACC, and activated SIRT1–AMPK signaling, indicating a metabolic shift that reduces lipogenesis and enhances fatty-acid oxidation [1][6]. These mechanisms directly counteract oxidative injury and metabolic stress, key pathological drivers of NAFLD progression.

Comparable outcomes have been reported for *Caulerpa racemosa*. Dietary supplementation and sulfated polysaccharide fractions significantly reduced triglycerides, LDL cholesterol, and fasting glucose while

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

increasing HDL concentrations in cholesterol-fat enriched diet models [7][9]. Mechanistic analysis revealed modulation of the PRMT-1/DDAH/ADMA and mTOR–SIRT1–AMPK pathways, further supporting its role in restoring metabolic and endothelial homeostasis [7][9]. These targets overlap with those of established metabolic therapies, suggesting that *Caulerpa* may offer pharmacologically relevant benefits derived from natural sources.

A distinct advantage of *C. lentillifera* is its regulatory effect on the gut–liver axis, a central component in the transition from NAFLD to NASH. Findings from ethanol-induced liver injury models reported three major protective mechanisms [5]:

1. Anti-inflammatory regulation**:** *C. lentillifera* supplementation suppressed hepatic TLR4 signaling by downregulating TLR4, MyD88, and TRIF, which reduced the p-NF-κB/NF-κB ratio and lowered pro-inflammatory cytokines TNF-α and IL-1β.

2. Barrier function: Supplementation reversed the ethanol-induced decline of tight-junction proteins, strengthening intestinal barrier integrity and significantly decreasing circulating endotoxin.

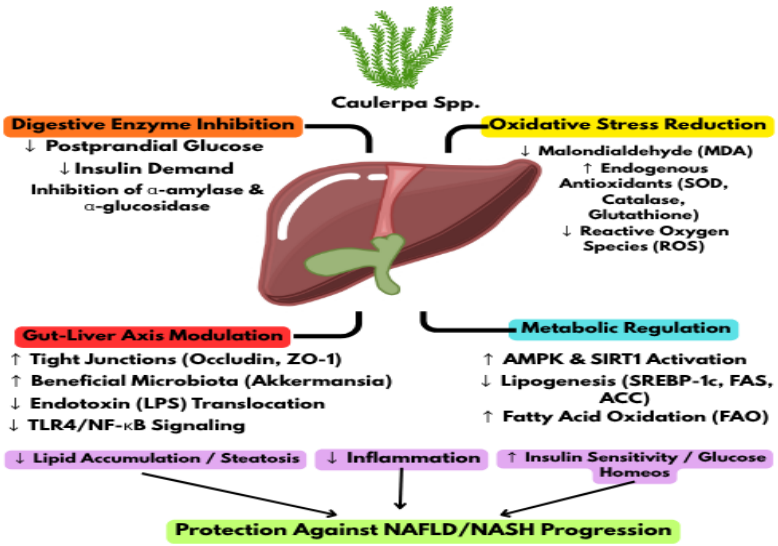
3. Microbiota modulation: *C. lentillifera* normalized the Firmicutes-to-Bacteroidetes ratio and increased beneficial taxa such as *Akkermansia*, which correlated positively with occludin and ZO-1 expression.

Additional studies involving *C.taxifolia* and *C.prolifera* demonstrate complementary antidiabetic and hepatoprotective effects. Sulfated galactans and phenolic constituents, including vanillin and kaempferol, inhibited α-amylase and α-glucosidase activity, improved insulin sensitivity, and reduced postprandial glucose [3][4]. Carotenoid- and peptide-rich fractions of *Caulerpa* also reduced body weight, hepatic lipid deposition, and blood glucose levels while enhancing microbiota diversity [2]. These combined antioxidant, antihyperglycemic, and microbiota-mediated effects align closely with the mechanistic requirements for slowing NAFLD progression and preventing transition to NASH.

Overall, *Caulerpa* spp. intervene at multiple critical stages of NAFLD pathophysiology, including metabolic regulation, oxidative stress reduction, inflammatory suppression, and stabilization of the gut liver axis., the inhibition of digestive enzymes such as *C. racemosa* extract demonstrating 81.67% inhibition of α- glucosidase and 84.07% inhibition of α- amylase, indicates significant antidiabetic potential. Other studies found *C. racemosa*'s ethyl acetate fraction effectively inhibited alpha-glucosidase with an IC50 value of 153.87 µg/ml, aligning with the therapeutic actions of standard antidiabetic drugs like acarbose.

Integrative Hepatoprotective Mechanisms of *Caulerpa* spp. Against NAFLD/NASH

Figure 2 Integrative Hepatoprotective Mechanisms



Given the multi-target biological activities demonstrated by *Caulerpa* spp. across the reviewed literature, an integrative mechanistic pathway diagram is essential to improve conceptual clarity and visually synthesize the

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

interconnected hepatoprotective and antihyperglycemic mechanisms. Prior figures in the manuscript separately illustrate oxidative stress reduction, modulation of lipid metabolism, enzyme inhibition, and microbiota regulation; however, presenting these mechanisms collectively will provide a more cohesive visualization of how *Caulerpa*-derived compounds act simultaneously on multiple organ systems. This integrative figure is particularly relevant for NAFLD/NASH, which itself is a multi-hit metabolic disorder involving gut dysbiosis, oxidative stress, inflammation, and impaired lipid metabolism.

The proposed schematic consolidates four major pathways consistently identified in *in vitro, in vivo,* and clinical studies:

(1) inhibition of digestive enzymes (α-amylase and α-glucosidase),

(2) modulation of gut microbiota and intestinal barrier integrity,

(3) attenuation of oxidative stress, and

(4) regulation of metabolic pathways via SIRT1–AMPK activation and lipogenic gene suppression.

The hepatoprotective mechanisms of *Caulerpa* spp. against Non-Alcoholic Fatty Liver Disease (NAFLD) and its inflammatory progression, Non-Alcoholic Steatohepatitis (NASH), are comprehensive, aligning with the hypothesis which posits that the disease arises from numerous, parallel insults [23]. *Caulerpa* exerts its protective effects not through a single target, but by simultaneously modulating four distinct, yet interconnected, pathways.

First, as an upstream intervention, *Caulerpa* addresses the initial metabolic burden originating from the diet. Bioactive compounds, including phenolics and polysaccharides, have been shown to effectively inhibit key digestive enzymes, specifically -amylase and -glucosidase [24]. This action slows the breakdown of complex carbohydrates in the gastrointestinal tract, leading to a blunted postprandial glucose spike. The immediate consequence is a reduced demand for insulin, which in turn mitigates a primary driver for *de novo* lipogenesis (the creation of new fat) in the liver.

Second, *Caulerpa* plays a crucial role in modulating the gut-liver axis, a critical communication highway that is often compromised in NAFLD [27]. Evidence from studies on *C. lentillifera* reveals a dual-action benefit: it enhances intestinal barrier integrity by upregulating the expression of tight-junction proteins like Occludin and ZO-1, and it concurrently fosters a healthier gut microbiome by enriching beneficial populations, such as *Akkermansia* [26]. This fortified barrier function significantly reduces the translocation of bacterial endotoxins (LPS) from the gut into the portal circulation. By preventing this "leaky gut" phenomenon, *Caulerpa* effectively diminishes the primary trigger for hepatic inflammation, dampening the TLR4/NF-B signaling cascade within liver cells.

Third, *Caulerpa* provides direct hepatocellular protection by combating oxidative stress, a key factor that propels the progression from simple fatty liver (steatosis) to the more dangerous inflammatory state of NASH [25]. The seaweed's compounds bolster the liver's endogenous antioxidant defense system, demonstrably increasing the activity of crucial enzymes like Superoxide Dismutase (SOD), Catalase, and Glutathione. Simultaneously, it significantly lowers levels of malondialdehyde (MDA), a key marker of lipid peroxidation and cellular damage [22]. This powerful antioxidant effect shields hepatocytes from damage by Reactive Oxygen Species (ROS), preserving cellular integrity and reducing a major source of inflammation.

Finally, at the core of liver metabolism, *Caulerpa* directly addresses the accumulation of fat by promoting metabolic regulation at the intracellular level. This is primarily achieved through the activation of the AMPK and SIRT1 signaling pathways, which act as master regulators of cellular energy homeostasis [28]. This activation initiates a critical metabolic shift: it actively *suppresses de novo* lipogenesis by downregulating the key transcription factors and enzymes responsible for fat synthesis (e.g., SREBP-1c, FAS, ACC), while it *simultaneously promotes* fatty acid oxidation (the "burning" of fat for energy).

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

In conclusion, the therapeutic potential of *Caulerpa* spp. for NAFLD/NASH lies in this synergistic, multi-target approach. By combining upstream digestive enzyme inhibition, restoration of the gut-liver axis, potent antioxidant defense, and a direct reprogramming of hepatic lipid metabolism, these pathways converge. The unified outcome is a significant reduction in lipid accumulation (steatosis), decreased hepatic inflammation, and improved systemic insulin sensitivity, all of which contribute to robust protection against the progression of NAFLD to NASH [23].

Limitation

Although the existing preclinical evidence is promising, several significant limitations must be addressed before the clinical potential of *Caulerpa* can be realized. First, the clinical data gap is substantial; this review identified only one human clinical trial , which focused on obesity rather than diagnosed NAFLD or NASH patients.

Second, pharmacokinetic and bioavailability (PK/PD) challenges were unexplored in the existing studies. Key bioactive compounds, such as sulfated polysaccharides, are large macromolecules generally known for poor oral bioavailability. Future studies must quantify the absorption of these compounds and their concentrations in liver tissue to validate that effective doses are systemically achievable. Third, the extreme dose heterogeneity in *in vivo* studies (ranging from 65 mg/kg to 50 g/kg diets) makes the determination of a *human-equivalent dose* (HED) nearly impossible. The high doses used in some animal models may not be practical or tolerable for chronic supplementation in humans. Finally, toxicological and long-term safety considerations are entirely unaddressed. While *Caulerpa* is edible, some species (particularly invasive strains) are known to accumulate heavy metals or produce toxic secondary metabolites like *caulerpicin* and *caulerpenyne* as defense mechanisms. The lack of formal long-term toxicology studies is a major barrier to regulatory approval as a nutraceutical. Therefore, extraction standardization, phytochemical profiling, and rigorous safety assessments are urgently required.

Future Research

To translate these promising preclinical findings into viable nutraceuticals or therapeutics, several key industrial and research challenges must be addressed.

Extraction Standardization and Quality Control

A primary challenge is the lack of standardization. As seen in the reviewed studies, extraction methods vary widely (e.g., different solvent macerations vs. Soxhlet), directly impacting the bioactive profile and potency. Commercial development demands the establishment of validated, standardized green extraction protocols. Furthermore, phytochemical fingerprinting (e.g., using HPLC or GC-MS) is essential to establish a consistent compound profile and ensure batch-to-batch quality.

Scalability and Sustainability

Reliance on wild harvesting of *Caulerpa* is neither sustainable nor scalable for mass production. Industrial scalability is entirely dependent on optimizing aquaculture techniques. Future research should focus on improving cultivation yields while rigorously monitoring for potential contaminant accumulation (like heavy metals) from seawater to ensure product safety.

Formulation and Delivery

Overcoming poor bioavailability (as discussed in Limitations) is critical for efficacy. Research must focus on advanced formulations. Technologies such as nanoencapsulation or biopolymer delivery systems are crucial for protecting bioactive compounds from degradation, enhancing solubility, and ensuring targeted delivery, thereby improving overall bioefficacy.

Clinical Validation

Ultimately, all these efforts must culminate in larger, well-designed, multi-center randomized controlled trials

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(RCTs) in diagnosed NAFLD and NASH patient populations to validate safety, efficacy, and optimal dosage in the target population.

Industrial Implications: Scalability, Standardization, and Sustainability

The therapeutic potential of *Caulerpa* spp. for metabolic liver disease must also be evaluated through the lens of industrial feasibility. In order for *Caulerpa*-derived extracts to progress from preclinical studies to commercial nutraceutical or pharmaceutical products, several large-scale challenges including extraction standardization, production scalability, and sustainability must be systematically addressed. These considerations are essential to ensure consistency, safety, and economic viability for future clinical and industrial applications.

Extraction Standardization and Quality Control

Current findings reveal substantial heterogeneity in extraction methods across studies, resulting in wide variation in phytochemical profiles and bioactivity. Most research employs different solvents (water, ethanol, methanol, ethyl acetate), extraction times, or temperatures, leading to inconsistent concentrations of key bioactive constituents such as sulfated polysaccharides, carotenoids, peptides, and polyphenols. This variability poses a major barrier to reproducibility and regulatory validation. Industrial translation therefore requires the establishment of standardized extraction protocols based on Good Manufacturing Practices (GMP) and green extraction technologies, including supercritical CO_2 extraction, microwave-assisted extraction, or ultrasound-assisted extraction. These approaches improve yield, reduce solvent waste, and preserve thermolabile compounds, making them ideal for large-scale production. Robust quality control must also be integrated using analytical techniques such as HPLC, LC–MS/MS, or GC–MS to generate a stable phytochemical fingerprint that ensures batch-to-batch consistency. This step aligns with regulatory expectations for botanical drug development, where marker compounds must be identified and quantified to guarantee product reliability [21].

Scalability and Aquaculture Requirements

Large-scale production of *Caulerpa* cannot depend solely on wild harvesting, as this raises concerns about ecological disturbance, seasonality, and variability in nutrient composition. Moreover, wild *Caulerpa* may accumulate environmental contaminants such as heavy metals, pesticides, or microplastics, which compromise extract safety and require extensive purification. To achieve industrial scalability, commercial development must shift toward controlled aquaculture systems, including tank-based cultivation, integrated multi-trophic aquaculture (IMTA), or long-line marine farming. These approaches allow for standardized nutrient conditions, controlled light and salinity, and continuous monitoring to avoid contaminant accumulation. Aquaculture-based production also ensures stable biomass supply while reducing ecological pressures on coastal ecosystems. Studies in seaweed biotechnology demonstrate that optimized aquaculture can increase biomass yield by 40–60% while improving polysaccharide uniformity and reducing heavy-metal uptake [29] Such models are directly applicable to *Caulerpa* spp. and necessary for its future commercialization.

Sustainability and Environmental Considerations

Sustainable production is especially important because certain *Caulerpa* species (e.g., *C. taxifolia*) are known to behave as invasive organisms in non-native waters. Large-scale harvesting without proper ecological assessment may risk habitat disturbance or biodiversity loss. Therefore, environmental risk assessment and Life Cycle Assessment (LCA) must be incorporated into cultivation planning to ensure low carbon footprint, low nutrient discharge, and minimal ecological disturbance. Additionally, valorization of residual biomass such as converting spent seaweed pulp into animal feed, compost, or biodegradable packaging may enhance sustainability and economic value, aligning with circular bioeconomy principles recommended by United Nations Environment Programme [30].

Formulation, Delivery, and Bioavailability Challenges

Even with scalable biomass production, formulation challenges remain. Bioactive polysaccharides from

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Caulerpa generally possess large molecular weights and limited gastrointestinal absorption. To improve oral bioavailability and therapeutic potency, advanced delivery systems including nanoencapsulation, liposomal carriers, or biopolymer-based hydrogels should be explored. These technologies can protect compounds from degradation, enhance solubility, and enable targeted hepatic delivery, improving overall clinical efficacy.

Translational and Regulatory Pathways

Finally, translational success will depend on rigorous toxicological evaluation, standardized dosage determination, and multi-center clinical trials. Regulatory agencies such as the FDA and EMA require comprehensive safety, pharmacokinetic, and manufacturing data before approving botanical therapeutics. Establishing standardized cultivation, extraction, and quality-control systems is therefore not only scientifically necessary but also essential for meeting regulatory benchmarks for future *Caulerpa*-based interventions.

CONCLUSION

This review demonstrates that *Caulerpa spp*. contains bioactive compounds with strong hepatoprotective and antihyperglycemic effects supported by *in vitro, in vivo*, and early clinical evidence. Through antioxidant activity, metabolic regulation, enzyme inhibition, and gut–liver axis modulation, *Caulerpa* effectively reduces oxidative stress, lipid accumulation, and glucose dysregulation, key of NAFLD and NASH progression. While findings are consistently positive, clinical research remains limited and extract standardization is still required. Future clinical trials are essential to evaluate long-term safety, establish clinically relevant therapeutic dosages, and determine if these preclinical findings can be effectively translated into nutraceuticals for metabolic liver disease.

Conflicts of Interest

The Authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

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The data supporting this paper is available in the cited references.

Ethical Approvals

Not applicable

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